ORIGINAL PAPER

Submitted: 07.09.2022
Accepted: 22.12.2022
Early publication date: 24.03.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0015
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 2/2023

Does total tumour diameter, multifocality, number of tumour foci, or laterality predict lymph node metastasis or recurrence in differentiated thyroid cancer?

Onur Elbasan[1], *Can Ilgın*[2], *Dilek Gogas Yavuz*[3]

[1]*Clinics of Endocrinology and Metabolism, Sinop Ataturk State Hospital Central/Sinop, Sinop, Türkiye*
[2] *Infectious Diseases and Environmental Health Division, Sirnak Province Health Directory, Turkish Ministry of Health, Şırnak, Türkiye*
[3]*Department of Endocrinology and Metabolism, Marmara University, School of Medicine, Istanbul, Türkiye*

Abstract

Introduction: Data regarding laterality, focality, or total tumour diameter (TTD) in papillary thyroid cancer (PTC) are limited. We aimed to investigate the impact of focality, TTD, number of tumour foci, or laterality on aggressive features in PTC.

Material and methods: Patients were categorized based on maximum tumour diameter (MTD) (≤ 10 *vs.* > 10 mm), focality, laterality, or the number of tumour foci (1/2/≥3). We also categorized the patients as follows: Group 1, unifocal microcarcinoma (MTD ≤ 10/TTD ≤ 10 mm); Group 2, multifocal microcarcinoma (MTD ≤ 10/TTD ≤ 10 mm); Group 3, multifocal microcarcinoma (MTD ≤ 10/TTD > 10 mm); Group 4, unifocal macrocarcinoma (MTD > 10/TTD > 10 mm); Group 5, multifocal macrocarcinoma (MTD > 10/TTD > 10 mm).

Results: The mean diagnosis age (n = 511) was 44.7 (± 12.7) years, the majority of the patients were < 55 years old (n = 310) and female (n = 416). An increasing number of tumour foci were associated with a higher MTD or TTD, a higher ratio of extrathyroidal extension (ETE), vascular or lymphatic invasion, lymph node metastasis (LNM) or distant metastasis, or the need for radioactive iodine (RAI). There was no difference in the parameters between Group 3 and Group 2, or Group 4. Vascular invasion, American Thyroid Association high risk, LNM at diagnosis, and RAI total dose were higher in Group 5 than in Group 3. Microscopic or macroscopic ETE, T1b, and T4a were positive predictors for recurrence. Male sex, multifocality, number of tumour foci (≥ 3), MTD (> 10 mm), TTD (> 10 mm), Group 5, microscopic or macroscopic ETE, lymphatic or vascular invasion, RAI need, T2, and T4b were positive predictors for LNM.

Conclusion: MTD and TTD increase the risk of LNM but not the recurrence in PTC. TTD, multifocality, and bilaterality can be considered risk factors in PTC staging systems and risk calculators. **(Endokrynol Pol 2023; 74 (2): 153–167)**

Key words: *thyroid; cancer; papillary; diameter; focality; laterality*

Introduction

Differentiated thyroid cancers (DTC) consists of more than 90% of all thyroid cancers [1]. A small number (10–15%) of DTC patients have an aggressive course leading to a poor prognosis [1, 2]. Tumour diameter, macroscopic extrathyroidal extension (ETE), and cervical lymph node metastasis (LNM) were defined in the 8th version of the American Joint Committee on Cancer Tumour, Node, Metastasis (AJCC TNM) staging system (AJCC 8) as important factors affecting the risk of recurrence/metastasis [3]. Additionally, in the American Thyroid Association (ATA) guidelines, aggressive histological subtypes (e.g. tall cells or columnar cell variants) and specific molecular profiles (e.g. BRAF mutations) were defined as unfavourable regarding the risk of recurrence/metastasis [1].

The prevalence of multifocal DTC ranges from 18% to 87% in different series [4–13]. Multifocality was indicated to confer a low risk for persistence/recurrence in ATA guidelines [1]. These guidelines indicated that similar management strategies have been employed in patients with multifocal or unifocal microcarcinoma, and that the number of tumour foci was not associated with worse prognosis in microcarcinoma [1, 14]. However, in some studies, multifocality in DTC is associated with aggressive features, capsular invasion, vascular invasion, LNM, advanced stage, recurrence-free survival (RFS), and disease-specific survival (DSS) [4, 6–9, 15].

In multifocal DTC, tumoural lesions other than the primary tumour may be too small to be diagnosed before thyroidectomy and can be revealed only by pathological analysis of the whole specimen. In AJCC 8, the tumour diameter was based on the largest tu-

Onur Elbasan, 1 Sinop Ataturk State Hospital, Clinics of Endocrinology and Metabolism, Sinop Ataturk State Hospital Central/Sinop, Sinop, Türkiye; e-mai: dronurelbasan@hotmail.com

moural lesion independently of the number of tumoural lesions [16]. The percentage of patients with multifocal DTC consisting of a maximum tumour diameter (MTD) of < 1 cm among all patients with DTC was less than half in some studies but higher than half in others [7–13]. The effect of co-existent tumoural lesions other than the largest tumour in multifocal DTC on aggressive behaviour has not been studied. In a limited number of studies, it was shown that multifocal papillary thyroid microcarcinoma with a total tumour diameter (TTD) > 1 cm might have more aggressive features than unifocal papillary microcarcinoma [4, 11]. There are also limited data regarding the effect of laterality (unilateral *vs*. bilateral) on the recurrence in multifocal DTC [5, 11, 12].

We aimed to investigate the impact of multifocality, TTD, number of tumour foci, or laterality of tumour on aggressive behaviour, recurrence, and lymph node metastasis in patients with DTC.

Material and methods

Study design

This retrospective study was conducted at the Marmara University Pendik Training and Research Hospital, and it was approved by the local Ethics Committee of Marmara University; approval number 09.2021.622. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The adult patients diagnosed with papillary thyroid carcinoma (PTC) and followed up for at least one year between January 2010 and December 2019 were analysed retrospectively.

Data collection

Demographic parameters (age, age at diagnosis, and sex), clinical parameters such as duration of follow-up and radioactive iodine (RAI; absence *vs.* presence and the dose), and findings of imaging methods (neck sonography and whole-body iodine scan [WBS]) were recorded. Pathological findings (type and pathological variant of thyroid cancer, primary localization, laterality [unilateral *vs.* bilateral], multifocality [unifocal *vs.* multifocal], number of tumour foci, diameter of each tumour focus, MTD [≤ 10 mm *vs.* > 10 mm], TTD [≤ 10 mm *vs.* >10 mm], microscopic and macroscopic extrathyroidal tissue invasion [ETE], and vascular or lymphatic invasion), and molecular findings (BRAF mutation [absent *vs.* present *vs.* unknown]), were recorded from electronic and written patient files, retrospectively.

Bilaterality was defined as detecting tumour foci in both lobes of the surgical specimen of the thyroid gland by pathological examination. Unifocality was defined as detecting only one tumour focus in the surgical specimen of the thyroid gland by pathological examination, and multifocality as the presence of ≥ 2 tumour foci. Microcancer and macrocancer were defined as MTD ≤ 10 mm and > 10 mm, respectively. Laboratory parameters (thyroid-stimulating hormone [TSH], free T4 [fT4], thyroglobulin [Tg], and antithyroglobulin antibody [TgAb] values measured in the routine follow-up) at baseline and in the follow-up were recorded retrospectively from the recordings. LNM or distant metastases at diagnosis were recorded. Follow-up features such as metastases (absence *vs.* presence, localization [central and/or lateral lymph node *vs.* distant metastasis], and time of onset), recurrence and/or persistence (absence *vs.* presence), and RAI treatment were also recorded. The method of molecular analysis used to identify somatic BRAF mutations has been defined in a previous report [17].

Surgical approach

The routine surgical procedure in the patients included in the study was total thyroidectomy plus prophylactic central neck dissection. Simultaneous lateral neck dissection was performed in patients with clinically positive lateral lymph node metastasis. Patients with unilateral resection, with previous history of thyroid or neck surgery or previous neck irradiation, with poorly differentiated pathology and/or incomplete pathological reports or missing data were excluded.

Radioactive iodine ablation

RAI was given 4-6 weeks after surgery to the patients with an intermediate or high risk according to guidelines [1]. The ^{131}I ablation dose was 100 mCi (millicuries) for almost all patients. Withdrawal of L-thyroxine replacement was used for the stimulation during iodine treatment in almost all patients. One week after ^{131}I administration, whole body scintigraphy (WBS) was performed. In persistent/recurrent disease with elevated serum Tg levels under LT4 suppressive therapy or TSH stimulation and/or high TgAb levels after the initial treatment, if significant uptake was detected in the thyroid bed by WBS, RAI treatment was repeated [18].

Staging and risk evaluation at the time of diagnosis

The staging was performed by using AJCC 8 systems [16]. To predict recurrence and/or persistence, patients were grouped according to the ATA risk stratification system based on ATA guidelines: ATA low risk, ATA intermediate risk, and ATA high risk [1].

Follow-up

A standard schedule including physical examination, neck sonography, and measurement of serum TgAb and Tg were performed in all patients under TSH suppression at 3-month intervals in the first year and annually after that [1]. If suspicious lesions were observed by neck sonography, fine-needle aspiration biopsy was used to confirm the neoplastic nature of thyroid and/or cervical lymph node. In case of clinical indication, additional imaging methods such as computed tomography, magnetic resonance imaging, and fluoro-18-deoxyglucose positron-emission tomography were used to detect potential distant non-radioiodine avid metastases.

Biochemical parameters

Serum TSH (range 0.34–5.6 μIU/mL), fT4 (range 0.61–1.12 ng/dL), Tg, and TgAb were measured in automated serum samples by the paramagnetic particle chemiluminescence immunoassay method (DxI800, Beckman Coulter, United States). The assay sensitivity limit was accepted as 0.2 for Tg and 0.9 for TgAb.

Persistence and recurrence

Remission was defined as undetectable suppressed Tg (< 0.2 ng/mL) and/or stimulated Tg of < 1 ng/mL in the absence of interfering TgAb and the absence of any evidence of tumour based on clinical or imaging findings [1,19]. Persistence and recurrence were defined as the presence of disease in the first year after the first treatment, and after at least a one-year disease-free period in DTC, respectively [20].

Demographic, clinical, pathological and molecular findings, stage, and recurrence risk based on ATA guidelines were compared between categories based on multifocality (unifocal *vs.* multifocal), laterality of tumour (unilateral *vs*. bilateral), or number of tumour foci (1 *vs.* 2 *vs.* ≥ 3). We also categorized the patients as follows: Group 1, unifocal microcarcinoma (MTD ≤ 10 mm, TTD ≤ 10 mm); Group 2, multifocal microcarcinoma (MTD ≤ 10 mm, TTD ≤ 10 mm);

Group 3, multifocal microcarcinoma (MTD ≤ 10 mm, TTD > 10 mm); Group 4, unifocal macrocarcinoma (MTD > 10 mm, TTD > 10 mm); and Group 5, multifocal macrocarcinoma (MTD > 10 mm, TTD > 10 mm). All data were analysed to detect the predictors for recurrence or LNM.

Statistical analysis

Data obtained in the study were analysed statistically using Stata 15.1 software (Stata Corporation LLC, November 2017, United States). The conformity of the data to normal distribution was evaluated using the Shapiro-Wilk Francia test. When comparing 2 independent groups of quantitative data according to each other, the Mann-Whitney U test was used. When comparing multiple independent groups of quantitative data according to each other as non-parametric tests, the Kruskal-Wallis H test was used, and Dunn's test was used for post hoc analyses. The homogeneity of categorical variables was evaluated by the chi-square test. When comparing categorical variables to each other, the Pearson chi-square and Fisher exact tests were used. The binary logistic regression test was used to measure the effects of predictors on recurrence or LNM. Due to the limited number of observations and high variance inflation between independent variables, a significant multivariate model could not be established. Kaplan-Meier (product limit method) log rank (Mantel-Cox) analysis was used to evaluate the effect of multifocality or bilaterality of the tumour, the number of tumour foci, and TTD on metastasis-free survival (MFS). Quantitative variables are stated as mean ± standard deviation (SD) and median (minimum-maximum) values, and categorical variables as number (n) and percentage (%) in the tables. Variables were evaluated at a 95% confidence level, and a value of $p < 0.05$ was accepted as statistically significant.

Results

Of the total (n = 511), the mean age was 44.7(± 12.7) years, and most of the patients were < 55 years old (n = 310) and female (n = 416). The tumour was multifocal in 30.7% (n = 157) and bilateral in 17.8% (n = 91) of the patients. LNM or distant metastasis at diagnosis was present in 12.5% (n = 64) and 1% (n = 5) of the patients, respectively. Recurrence/persistence was found in 18.6% (n = 95) of the patients (Tab. 1).

Age, sex, BRAF mutation positivity, stage, and recurrence/persistence did not differ between the patients with unifocal or multifocal tumours. MTD or TTD was higher in the multifocal tumour group than

Table 1. *Baseline demographic, clinical, and pathological features of the patients with differentiated thyroid cancer (DTC)*

Parameters	n (%)
Sex (female/male)	416/95 (81.4/18.6)
Age at diagnosis (≥ 55/< 55 years old)	201/310 (39.3/60.7)
MTD (≤ 10/> 10 mm)	275/236 (53.8/46.2)
TTD (≤ 10/> 10 mm)	303/208 (59.3/40.70)
Multifocal tumour	157 (30.7)
Bilateral tumour	91 (17.8)
Number of tumour foci	
1	354 (69.3)
2	92 (18.0)
≥ 3	65 (12.7)
Microscopic ETE (present/absent)	97/414 (19/81)
Macroscopic ETE (present/absent)	9/502 (1.8/98.2)
Vascular invasion (present/absent)	70/441 (13.7/86.3)
Lymphatic invasion (present/absent)	68/443 (13.3/86.7)
ATA risk	
Low	342 (66.9)
Intermediate	151 (29.6)
High	18 (3.5)
RAI	
RAI need	279 (54.6)
Recurrent RAI	37 (7.2)
LNM	
At diagnosis	64 (12.5)
At anytime	85 (16.6)
Central	61 (11.9)
Lateral	52 (10.2)
Both central and lateral	28 (5.5)
Distant metastasis at diagnosis	5 (1)
Distant metastasis at anytime	11 (2.2)
Recurrence/persistence	95 (18.6)
AJCC 8	
Stage 1/2/3/4	490/10/7/4 (95.9/1.9/1.4/0.8)
T1a/1b	239/171 (46.8/33.5)
T2	76 (14.9)
T3a/3b	16/- (3.1/-)
T4a/4b	6/3 (1.2/0.6)
N0/N1a/N1b	447/30/34 (87.5/5.9/6.6)
M0/M1	507/4 (99.2/0.8)
BRAF (positive/negative/unknown)	21/31/459 (4.1/6.1/89.8)
	Mean (± SD)
Age at diagnosis [year]	44.7 ± 12.7
	Median (Min.-Max.)
Age (year)	51 (19–88)
Duration of follow-up [months]	36 (12–120)
MTD [mm]	11 (0.4–110)
TTD [mm]	13 (0.4–135)
RAI total dose [mCi]	100 (30–600)

TT — total thyroidectomy; PTC — papillary thyroid cancer; FTC — follicular thyroid cancer; MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; ATA — American Thyroid Association; RAI — radioactive iodine; LNM — lymph node metastasis; AJCC — American Joint Committee on Cancer; Min. — minimum; Max. — maximum

in the unifocal group. The percentage of patients with microscopic ETE was higher in the multifocal tumour group than in the unifocal tumour group ($p < 0.001$), but macroscopic ETE was similar in both groups ($p = 0.174$). The percentage of patients with vascular or lymphatic invasion was higher in the multifocal tumour group ($p = 0.003$, $p < 0.001$, respectively). The percentage of patients with ATA high risk was higher in the multifocal tumour group ($p < 0.001$). The percentage of patients with RAI need, metastasis, LNM, or distant metastasis was significantly higher in the multifocal tumour group (Tab. 2).

Age, sex, BRAF mutation, stage, recurrence/persistence, and metastasis did not differ between the patients with unilateral or bilateral tumours. The number of tumour foci was significantly higher in the bilateral tumour group ($p < 0.001$). MTD or TTD was higher in the bilateral tumour group than in the unilateral tumour group. The percentage of patients with microscopic or macroscopic ETE was higher in the bilateral tumour group than in the unilateral tumour group ($p = 0.023$, $p = 0.035$, respectively). The percentage of patients with vascular or lymphatic invasion was higher in the bilateral tumour group ($p = 0.004$, $p = 0.002$, respectively). The percentage of patients with ATA high risk was higher in the bilateral tumour group ($p < 0.001$). The percentage of the patients with RAI need or LNM at diagnosis was significantly higher in the bilateral tumour group (Tab. 2).

Of patients with multifocal DTC ($n = 157$), 58% ($n = 91$) had bilateral multifocal DTC. Demographic, clinical, and pathological features did not differ between the patients with unilateral multifocal DTC and those with bilateral multifocal DTC, except for TTD (Tab. 3).

Of the total, 12.7% ($n = 65$) had ≥ 3 DTC foci. The increasing number of tumour foci was associated with higher MTD or TTD, a higher ratio of ETE, vascular or lymphatic invasion, LNM or distant metastasis, higher ATA risk and stage, or RAI need (Tab. 4). BRAF mutation was positive in 11 patients with one foci, 5 patients with 2 foci, and 5 patients with ≥ 3 foci ($p = 0.294$) (not shown on the tables).

RAI need and RAI total dose were higher in Group 3 compared to those in Group 1. There was no difference regarding demographic, clinical, and pathological features between Group 3 and Group 2, or Group 4. Vascular invasion, ATA high risk, LNM at diagnosis, and RAI total dose were higher in Group 5 than in Group 3 (Tab. 5).

Microscopic ETE, macroscopic ETE, T1b, T4a, and T-Total T1b were important positive predictors for recurrence (Tab. 6). Male sex, multifocality, number of tumour foci (≥ 3), MTD (> 10 mm), TTD (> 10 mm), Group 5, microscopic ETE, macroscopic ETE, lymphatic invasion, vascular invasion, RAI need, T2, T4b, and T-Total T2 were positive predictors for LNM (Tab. 7).

Kaplan-Meier RFS estimates of LNM regarding focality, laterality, number of tumour foci, or Groups are shown in Figure 1. The ratio of occurrence of LNM in 5 years of follow-up was 13.8% in patients with unifocal tumours (MFS: 86.2%), 22.9% in those with multifocal tumours (MFS: 77.1%), 15.5% in those with unilateral tumours (MFS: 84.5%), and 22% in those with bilateral tumours (MFS: 78%). It was 13.8% in those with one tumour focus (MFS: 86.2%), 15.2% in those with 2 tumour foci (MFS: 84.8%), and 33.9% in those with ≥ 3 tumour foci (MFS: 66.1%). It was 11% in Group 1 (MFS: 89%), 11.5% in Group 2 (MFS: 88.5%), 14.3% in Group 3 (MFS: 85.7%), 16.9% in Group 4 (MFS: 83.1%), and 28.2% in Group 5 (MFS: 71.8%). We found a cut-off value of 14.5 mm for TTD in predicting LNM [area under curve (AUC): 0.6212, sensitivity: 0.66, specificity: 0.57, $p < 0.001$] (Fig. 2).

Discussion

We showed that bilaterality or multifocality was associated with higher MTD or TTD, microscopic ETE, vascular or lymphatic invasion, ATA high risk, RAI need, and LNM. Vascular invasion and LNM at diagnosis were more frequent, and ATA high risk and RAI dose were higher in Group 5 than in Group 3. Multifocality, MTD (> 10 mm), and TTD (> 10 mm) increased the risk of LNM 1.85, 2.07, and 2.07-fold, respectively, but were not a positive predictor of recurrence. Bilaterality was not a predictor for recurrence or LNM.

We showed that about one-third of our patients did have multifocal tumours, about one-fifth bilateral tumours, and in multifocal DTC patients, about one-fifth showed recurrence. The findings were consistent with previous reports indicating a range for the ratio of multifocality of 18–87%, and that of bilaterality of 13–56% [7–9, 11, 21]. Due to the scantness of the evidence, current staging or risk stratification systems have not considered multifocality or bilaterality as a risk factor for recurrence [1, 16]. In one study analysing 2390 patients with PTC, multifocality was associated with LNM, ETE, and higher tumour size [7]. Multifocality, but not bilaterality, was shown as a predictor of RFS in that cohort. In multivariate analysis, multifocality remained a significant predictor. The study showed that multifocality increased the risk of recurrence 1.93-fold, and that the 5-year RFS rate was 99.4% in unifocal and 97.7% in multifocal PTC ($p < 0.005$). We showed a MFS of 86.2% in unifocal and 77.1% in multifocal PTC. In another study, similarly, multifocality but not bilaterality was an important factor for RFS in patients with DTC ($p = 0.042$) [8].

Table 2. *Comparison of the patients' demographic, clinical, and pathological features with unifocal and multifocal differentiated thyroid cancer (DTC), and with unilateral and bilateral DTC*

	Unifocal DTC (n = 354)	Multifocal DTC (n = 157)	p-value	Unilateral DTC (n = 420)	Bilateral DTC (n = 91)	p-value
Parameters	**n (%)**			**n (%)**		
Sex (female/male)	294 (83.1)	122 (77.8)	0.152	346 (82.4)	70 (76.9)	0.225
Age at diagnosis (≥ 55/< 55 years)	74/280 (20.9/79.1)	38/119 (24.2/75.8)	0.405	92/328 (21.9/78.1)	20/71 (22/78)	0.988
Number of tumour foci (2/≥ 3)	–	–		43/23 (10.2/5.5)	49/42 (53.8/46.2)	< 0.001
MTD (≤ 10/> 10 mm)	182/172 (51.4/48.6)	54/103 (34.4/65.6)	< 0.001	205/215 (48.8/51.2)	31/60 (34.1/65.9)	0.011
TTD (≤ 10/> 10 mm)	182/172 (51.4/48.6)	26/131 (16.6/83.4)	< 0.001	192/228 (45.7/54.3)	16/75 (17.6/73.4)	< 0.001
Microscopic ETE (present)	52 (14.7)	45 (28.7)	< 0.001	72 (17.1)	25 (27.5)	0.023
Macroscopic ETE (present)	4 (1.1)	5 (3.2)	0.142	5 (1.2)	4 (4.4)	0.035
Vascular invasion (present)	38 (10.7)	32 (20.4)	0.003	49 (11.7)	21 (23.1)	0.004
Lymphatic invasion (present)	33 (9.3)	35 (22.3)	< 0.001	47 (11.2)	21 (23.1)	0.002
ATA Risk			< 0.001			< 0.001
Low	259 (73.2)	83 (52.9)		292 (69.5)	50 (54.9)	
Intermediate	89 (25.1)	62 (39.5)		119 (28.3)	32 (35.2)	
High	6 (1.7)	12 (7.6)		9 (2,2)	9 (9.9)	
RAI need	170 (48)	109 (69.4)	< 0.001	215 (51.2)	64 (70.3)	0.001
Metastasis	52 (14.7)	40 (25.5)	0.003	70 (16.7)	22 (24.2)	0.091
LNM at diagnosis	33 (9.3)	31 (19.7)	0.001	45 (10.7)	19 (20.9)	0.008
LNM at anytime	49 (13.8)	36 (22.9)	0.011	65 (15.5)	20 (22)	0.131
Central LNM	30 (8.5)	31 (19.7)	< 0.001	42 (10)	19 (20.9)	0.004
Lateral LNM	29 (8.2)	23 (14.6)	0.026	37 (8.8)	15 (16.5)	0.028
Both central and lateral LNM	10 (2.8)	18 (11.5)	< 0.001	14 (3.3)	14 (15.4)	< 0.001
Distant metastasis at diagnosis	1 (0.3)	4 (2.5)	0.033	3 (0.7)	2 (2.2)	0.218
Distant metastasis at anytime	4 (1.1)	7 (4.5)	0.040	7 (1.7)	4 (4.4)	0.114
Recurrence/persistence	65 (18.4)	30 (19.1)	0.841	78 (18.6)	17 (18.7)	0.981
AJCC 8						
Stage 1/2/3/4	344/6/4/0 (97.2/1.7/1.1/–)	146/4/3/4 (93/2.5/2/2.5)	0.031	405/9/5/1 (96.5/2.1/1.2/0.2)	85/1/2/3 (93.4/1.1/2.2/3.3)	0.033
BRAF mutation (positive)	11 (3.1)	10 (6.4)	0.182	14 (3.3)	7 (7.7)	0.033
	Median (Min.–Max.)			**Median (Min.–Max.)**		
Age at diagnosis [years]	44 (8–78)	45 (16–74)	0.254	44 (8–78)	44 (19–72)	0.884
Age [years]	51 (19–88)	51 (20–78)	0.716	51 (19–88)	49 (20–75)	0.329
Number of tumour foci				1 (1–8)	2 (1–8)	< 0.001
MTD [mm]	10 (0.4–100)	12 (3–110)	0.004	11 (0.4–100)	13 (3–110)	0.003
TTD [mm]	10 (0.4–100)	20 (4–135)	< 0.001	12 (0.4–100)	26 (4–135)	< 0.001
RAI total dose [mCi]	100 (30–600)	100 (50–600)	0.330	100 (30–600)	100 (50–600)	0.512

MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; ATA — American Thyroid Association; RAI — radioactive iodine; LNM — lymph node metastasis; AJCC — American Joint Committee on Cancer; Min. — minimum; max. — maximum

Kim et al. showed that multifocality, but not bilaterality, was a significant predictor of recurrence/persistence in a large patient population (n = 2095) with PTC [10]. They showed that multifocality increased the risk of recurrence/persistence 1.45-fold. Some studies failed to show any association of recurrence with multifocality or bilaterality in PTC [22, 23]. In our study, multifocality or bilaterality did not predict disease recurrence

Table 3. *Comparison of demographic, clinical, and pathological features of the patients with unilateral and bilateral multifocal differentiated thyroid cancer (DTC)*

	Unilateral multifocal DTC (n = 66)	Bilateral multifocal DTC (n = 91)	p-value
Parameters	**n (%)**		
Sex (female)	52 (78.8)	70 (76.9)	0.782
Age at diagnosis (≥ 55/< 55 years)	18/48 (27.3/72.7)	20/71 (22/78)	0.445
Number of tumour foci (2/≥ 3)	43/23 (65.2/34.9)	49/42 (53.9/46.1)	0.156
MTD (≤ 10/> 10 mm)	23/43 (34.9/65.2)	31/60 (34.1/65.9)	0.919
TTD (≤ 10/> 10 mm)	10/56 (15.1/84.9)	16/75(17.6/82.4)	0.686
Microscopic ETE (present)	20 (30.3)	25 (27.5)	0.699
Macroscopic ETE (present)	1 (1.5)	4 (4.4)	0.399
Vascular invasion (present)	11 (16.7)	21 (23.1)	0.325
Lymphatic invasion (present)	14 (21.2)	21 (23.1)	0.782
ATA risk			0.298
Low	33 (50)	50 (54.9)	
Intermediate	30 (45.5)	32 (35.2)	
High	3 (4.5)	9 (9.9)	
RAI need	45 (68.2)	64 (70.3)	0.773
Metastasis	18 (27.3)	22 (24.2)	0.660
LNM at diagnosis	12 (18.2)	19 (20.9)	0.675
LNM at anytime	16 (24.2)	20 (22)	0.739
Central LNM	12 (18.2)	19 (20.9)	0.675
Lateral LNM	8 (12.1)	15 (16.5)	0.445
Both central and lateral LNM	4 (6.1)	14 (15.4)	0.080
Distant metastasis at diagnosis	2 (3)	2 (2.2)	1.000
Distant metastasis at anytime	3 (4.6)	4 (4.4)	1.000
Recurrence/persistence	13 (19.7)	17 (18.7)	0.873
AJCC 8			
Stage 1/2/3/4	61/3/1/1 (92.4/4.6/1.5/1.5)	85/1/2/3 (93.4/1.1/2.2/3.3)	0.590
BRAF mutation (positive)	3 (4.6)	7 (7.7)	0.178
	Median (Min.-Max.)		
Age at diagnosis [year]	45.5 (16–74)	44 (19–72)	0.377
Age [year]	51 (23–78)	49 (20–75)	0.301
Number of tumour foci	2 (2–8)	2 (2–8)	0.110
MTD [mm]	11.5 (3–60)	13 (3–110)	0.127
TTD [mm]	17 (5–75)	26 (4–135)	0.006
RAI total dose [mCi]	150 (50–400)	100 (50–600)	0.969

MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; ATA — American Thyroid Association; RAI — radioactive iodine; LNM — lymph node metastasis; AJCC — American Joint Committee on Cancer; Min. — minimum; Max. — maximum

in DTC. Multifocality was found not to be associated with recurrence in one study analysing PTC [11]. Our findings suggest that bilaterality or multifocality was associated with a higher MTD, TTD, microscopic ETE, vascular or lymphatic invasion, ATA high risk, RAI need, and LNM. The association of multifocality or bilaterality with ETE, vascular invasion, LNM, tumour size, RAI need, or TNM staging was also shown in other studies [4, 8–11]. In many studies, capsular invasion or TNM staging was investigated for its association with multifocality in PTC [8, 10, 11]. Detection of multifocality in the preoperative period is difficult in patients with DTC. Given the high ratio of multifocality, we tend to perform TT in patients. The ratio of patients given RAI was lower than that in previous studies, in which it was about 80–90% [7, 10–12]. This may indicate that those patients who underwent TT and received RAI had a lower actual risk for recurrence than expected.

Table 4. *Comparison of demographic, clinical, and pathological features of the patients with differentiated thyroid cancer (DTC) according to the number of tumour foci*

	Number of tumour foci			
	1 (n = 354)	**2 (n = 92)**	**≥ 3 (n = 65)**	**p-value**
Parameters		**n (%)**		
Sex (female)	294 (83.1)	76 (82.6)	46 (70.8)	0.061
Age at diagnosis (≥ 55/< 55 years)	74/280 (20.9/79.1)	20/72 (21.7/78.3)	18/47 (27.7/72.3)	0.477
MTD (≤ 10/> 10 mm)	182/172 (51.4/48.6)	33/59 (35.9/64.1)	21/44 (32.3/67.7)	0.002
TTD (≤ 10/> 10 mm)	182/172 (51.4/48.6)	22/70 (23.9/76.1)	4/61 (6.2/93.8)	< 0.001
Microscopic ETE (present)	52 (14.7)	27 (29.4)	18 (27.7)	0.001
Macroscopic ETE (present)	4 (1.1)	1 (1.1)	4 (6.2)	0.031
Vascular invasion (present)	38 (10.7)	18 (19.6)	14 (21.5)	0.013
Lymphatic invasion (present)	33 (9.3)	16 (17.4)	19 (29.2)	< 0.001
ATA risk				< 0.001
Low	259 (73.2)	51 (55.4)	32 (49.2)	
Intermediate	89 (25.1)	38 (41.3)	24 (36.9)	
High	6 (1.7)	3 (3.3)	9 (13.9)	
RAI need	170 (48.0)	60 (65.2)	49 (75.4)	< 0.001
Metastasis	52 (14.7)	16 (17.4)	24 (36.9)	< 0.001
LNM at diagnosis	33 (9.3)	13 (14.1)	18 (27.7)	< 0.001
LNM at anytime	49 (13.8)	14 (15.2)	22 (33.8)	< 0.001
Central LNM	30 (8.5)	11 (12)	20 (30.8)	< 0.001
Lateral LNM	29 (8.2)	9 (9.8)	14 (21.5)	0.005
Central and lateral LNM	10 (2.8)	6 (6.5)	12 (18.5)	< 0.001
Distant metastasis at diagnosis	1 (0.3)	1 (1.1)	3 (4.6)	0.005
Distant metastasis at anytime	4 (1.1)	1 (1.1)	6 (9.2)	0.002
Recurrence/persistence	65 (18.3)	14 (15.2)	16 (24.6)	0.323
AJCC 8				
Stage 1/2/3/4	344/6/4/0 (97.2/1.7/1.1/–)	88/2/0/2 (95.6/2.2/0/2.2)	58/2/3/2 (89.2/3.1/4.6/3.1)	0.010
		Median (Min.–Max.)		
Age at diagnosis [years]	44 (8–78)	42.5 (16–74)	48 (19–71)	0.214
Age [years]	51 (19–88)	48 (20–78)	52 (25–73)	0.319
Tumour diameter [mm]				
MTD	10 (0.4–100)	12.5 (3–85)	12 (3–110)	0.014
TTD	10 (0.4–100)	16 (4–135)	27 (4–121)	< 0.001
RAI total dose [mCi]	100 (30–600)	100 (50–300)	100 (50–300)	0.474

MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; ATA — American Thyroid Association; RAI — radioactive iodine; LNM — lymph node metastasis; AJCC — American Joint Committee on Cancer; Min. — minimum; Max. — maximum

We found that microscopic or macroscopic ETE were predictors for recurrence in all patients. Analysis of predictors for recurrence in subgroups of patients with PTC has acquired greater prominence in some studies [7, 8]. In one study analysing RFS in PTC subgroups, multifocality was not a predictor for RFS in multivariate analysis in the microcarcinoma group [7]. However, another report showed that multifocality was a significant predictor for recurrence also in the microcarcinoma subgroup of patients with PTC [8].

Tumours with ≥ 3 foci were detected in 12.7% of the patients in our study, and the ratio varied (6–13.7%) across the literature [6, 8, 11]. Similarly to our findings, previous studies reported that a higher number of tumour foci was associated with ETE, vascular invasion, LNM, or recurrence [6, 8, 11, 13]. Where the number of

Table 5. *Comparison of demographic, clinical and pathological features of the patients with differentiated thyroid cancer (DTC) according to maximum tumour diameter (MTD) and total tumour diameter (TTD)*

	Microcarcinoma (MTD ≤ 10 mm) (n = 237)			p-value	Macrocarcinoma (MTD > 10 mm, TTD > 10 mm) (n = 289)		p-value	Group 3 (n = 28) in comparison with			
	Group 1 (n = 182) Unifocal, TTD ≤ 10 mm	Group 2 (n = 26) Multifocal, TTD ≤ 10 mm	Group 3 (n = 28) Multifocal, TTD > 10 mm		Group 4 (n = 172) Unifocal	Group 5 (n = 103) Multifocal		Group 1	Group 2	Group 4	Group 5
Parameters	n (%)				n (%)			p-value			
Age at diagnosis (≥ 55/< 55 years)	37/145 (20.3/79.7)	5/21 (19.2/80.8)	7/21 (25/75)	0.834	37/135 (21.5/78.5)	26/77 (25.2/74.8)	0.476	0.572	0.610	0.679	0.979
ETE											
Microscopic (present)	17 (9.3)	4 (15.4)	5 (17.9)	0.307	35 (20.4)	36 (34.9)	0.007	0.185	1.000	1.000	0.084
Macroscopic (present)	0	0	0	–	4 (2.3)	5 (4.8)	0.302	–	–	–	–
Vascular invasion (present)	6 (3.3)	3 (11.5)	2 (7.1)	0.075	32 (18.6)	27 (26.2)	0.137	0.289	0.663	0.178	0.031
Lymphatic invasion (present)	14 (7.7)	2 (7.7)	4 (14.3)	0.455	19 (11.1)	29 (28.2)	< 0.001	0.272	0.670	0.538	0.134
ATA Risk				0.347			< 0.001	0.223	0.893	0.794	0.014
Low	148 (81.3)	19 (73.1)	20 (71.4)		111 (64.5)	44 (42.7)					
Intermediate	34 (18.7)	7 (26.9)	8 (28.6)		55 (32)	47 (45.6)					
High	0	0	0		6 (3.5)	12 (11.6)					
RAI need	45 (24.7)	14 (53.9)	20 (71.4)	< 0.001	125 (72.7)	75 (72.8)	0.980	< 0.001	0.181	0.891	0.884
Metastasis	22 (12.1)	4 (15.4)	4 (14.3)	0.863	30 (17.4)	32 (31.1)	0.009	0.758	1.000	0.793	0.078
LNM at diagnosis	13 (7.1)	3 (11.5)	2 (7.1)	0.728	20 (11.6)	26 (25.2)	0.003	1.000	0.663	0.745	0.038
LNM at anytime	20 (11)	3 (11.5)	4 (14.3)	0.878	29 (16.9)	29 (28.2)	0.026	0.536	1.000	1.000	0.134
Central LNM	14 (7.7)	3 (11.5)	4 (14.3)	0.460	16 (9.3)	24 (23.3)	0.001	0.272	1.000	0.493	0.302
Lateral LNM	11 (6)	1 (3.8)	2 (7.1)	0.892	18 (10.4)	20 (19.4)	0.037	0.686	1.000	0.746	0.159
Central and Lateral LNM	5 (2.7)	1 (3.8)	2 (7.1)	0.339	5 (2.9)	15 (14.6)	0.001	0.236	1.000	0.254	0.525
Distant metastasis at diagnosis	0	0	0	-	1 (0.6)	4 (3.9)	0.067	-	-	-	-
Distant metastasis at anytime	2 (1.1)	0	1 (3.6)	0.543	2 (1.2)	6 (5.8)	0.056	0.35	-	0.366	1.000
Recurrence/persistence	42 (23.1)	7 (26.9)	2 (7.1)	0.127	23 (13.4)	21 (20.4)	0.125	0.054	0.072	0.540	0.159

→

Table 5. *Comparison of demographic, clinical and pathological features of the patients with differentiated thyroid cancer (DTC) according to maximum tumour diameter (MTD) and total tumour diameter (TTD)*

	Microcarcinoma (MTD ≤ 10 mm) (n = 237)				Macrocarcinoma (MTD > 10 mm, TTD > 10 mm) (n = 289)			Group 3 (n = 28) in comparison with			
	Group 1 (n = 182) Unifocal, TTD ≤ 10 mm	Group 2 (n = 26) Multifocal, TTD ≤ 10 mm	Group 3 (n = 28) Multifocal, TTD > 10 mm	p-value	Group 4 (n = 172) Unifocal	Group 5 (n = 103) Multifocal	p-value	Group 1	Group 2	Group 4	Group 5
	Median (Min.–Max.)				Median (Min.–Max.)			p-value			
At diagnosis [years]	44 (18–78)	43 (22–64)	49.5 (30–71)	0.279	43.5 (8–77)	45 (16–74)	0.301	0.138	0.153	0.095	0.320
Age [years]	52 (20–88)	49 (29–69)	51 (34–75)	0.726	49 (19–77)	49 (20–78)	0.828	0.891	0.494	0.173	0.319
RAI total dose [mCi]	110 (30–300)	100 (50–230)	100 (50–400)	0.052	100 (30–600)	150 (50–600)	0.01	0.017	0.294	0.081	0.003

ETE — extrathyroidal extension; ATA — American Thyroid Association; RAI — radioactive iodine; LNM — lymph node metastasis; Min. — minimum; Max. — maximum

tumour foci was ≥ 3 the risk of LNM increased 3.18-fold in our study. Furthermore, we revealed the association of a higher number of tumour foci with higher MTD or TTD, lymphatic or vascular invasion, ATA high risk, RAI need, and distant metastasis. However, the number of tumour foci was not a significant predictor for recurrence. In a study analysing patients with PTC, patients with fewer tumour foci were found to have a higher RFS than that in those with a higher number of tumour foci (p = 0.028) [8]. In a study analysing a large population with PTC, the number of tumour foci predicted disease recurrence in a multifocal group of patients with PTC (p = 0.04) [10]. Another study revealed that the number of tumour foci (≥ 3) was related with decreased RFS (p = 0.001) and cancer-specific survival (p = 0.087) in PTC [6].

Although multifocality has not been included as a predictor for recurrence in the current staging or risk prediction systems, tumour size is involved [1, 16, 24]. However, MTD analysed in the pathological specimen defines the tumour size in multifocal tumours in these staging or risk prediction systems. The number of tumour foci was a significant predictor of recurrence in multifocal PTC [10]. However, the effect of TTD on outcomes in PTC, such as recurrence or LNM, has been less studied [11]. In our study, there was no difference between Groups 3 and 4 regarding age, ETE, lymphatic or vascular invasion, ATA risk category or RAI need. Zhao et al. revealed that the risk of LNM in microcarcinoma with a TTD > 10 mm was similar to that in macrocarcinoma [25]. We showed that ETE, lymphatic or vascular invasion, LNM or distant metastasis, or recurrence in Group 3 were similar to those in Group 2. Binary logistic regression analysis revealed that none of the groups was a predictor for recurrence, but in Group 5, the risk of LNM increased more than 3-fold. Similarly, Feng *et al*. showed in 442 patients with PTC that none of these groups predicted RFS, and in Groups 4 and 5 the risk of central LNM increased > 2-fold and the risk of lateral LNM > 4-fold [4]. In one study, capsular invasion, ETE, and LNM were higher in multifocal microcarcinoma with a TTD > 10 mm compared to multifocal microcarcinoma with a TTD ≤ 10 mm [11]. Another study showed no difference between these groups in terms of LNM [26]. We showed that TTD (> 10 mm) increased the risk of LNM 2.07-fold. It would be more informative to analyse the predictive value of TTD in a specific group of patients, such as those with microcarcinoma or unilateral DTC. In one study, ROC analysis showed a cut-off value of 40 mm for the sum of tumour foci diameters in predicting persistent/recurrent disease or disease-specific death (AUC: 0.793, p = 0.0002) [5]. They analysed the sum of tumour diameters only in participants with multifocal tumours, and the parameter had a high negative

Table 6. *Logistic regression analysis demonstrating the predictors of recurrence/persistence in differentiated thyroid cancer (DTC)*

		Recurrence/persistence		Univariate	
Parameters	**Present (n = 95)**	**Absent (n = 416)**	**p-value**	**OR (95% CI)**	**p-value**
		n (%)			
Sex (female/male)	76/19 (80/20)	340/76 (81.7/18.3)	0.696		
Age at diagnosis (≥ 55/< 55 years)	22/73 (23.2/76.8)	90/326 (21.6/78.4)	0.746		
Unilateral/Bilateral	78/17 (82.1/17.9)	342/74 (82.2/17.8)	0.981		
Unifocal/Multifocal	65/30 (68.4/31.6)	289/127 (69.5/30.5)	0.841		
Number of tumour foci (1/2/≥ 3)	65/14/16 (68.5/14.7/16.8)	289/78/49 (69.5/18.7/11.8)	0.323		
MTD (≤ 10/ > 10 mm)	51/44 (53.7/46.3)	185/231 (44.5/55.5)	0.104		
TTD (≤ 10/ > 10 mm)	30/65 (31.6/68.4)	96/320 (23.1/76.9)	0.083		
MTD, TTD and focality			0.053		
Group 1 MTD ≤ 10 mm, unifocal, TTD ≤ 10 mm	42 (44.2)	140 (33.6)			
Group 2 MTD ≤ 10 mm, multifocal, TTD ≤10 mm	7 (7.4)	19 (4.6)			
Group 3 MTD ≤ 10 mm, multifocal, TTD >10 mm	2 (2.1)	26 (6.3)			
Group 4 MTD > 10 mm, unifocal, TTD >10 mm	23 (24.2)	149 (35.8)			
Group 5 MTD > 10 mm, multifocal, TTD >10 mm	21 (22.1)	82 (19.7)			
Microscopic ETE (absent/present)	67/28 (70.5/29.5)	347/69 (83.4/16.6)	0.004	2.1 (1.26-3.5)	0.004
Macroscopic ETE (absent/present)	90/5 (94.7/5.3)	412/4 (99/1)	0.014	5.72 (1.51-21.73)	0.01
Vascular invasion (absent/present)	77/18 (81.1/18.9)	364/52 (87.5/12.5)	0.099		
Lymphatic invasion (absent/present)	78/17 (82.1/17.9)	365/51 (87.7/12.3)	0.145		
RAI need (absent/present)	42/53 (44.2/55.8)	190/226 (45.7/54.3)	0.796		
BRAF mutation (positive/negative/unknown)	3/5/87 (3.2/5.3/91.5)	18/26/372 (4.3/6.3/89.4)	0.810		
T			0.010		
T1a	53 (55.8)	186 (44.7)		1	
T1b	24 (25.3)	147 (35.3)		0.57 (0.34-0.97)	0.039
T2	12 (12.6)	64 (15.4)		0.66 (0.33-1.31)	0.233
T3a	1 (1)	15 (3.6)		0.23 (0.03-1.81)	0.164
T3b	0	0		NA	NA
T4a	4 (4.2)	2 (0.5)		7.02 (1.25-39.38)	0.027
T4b	1 (1)	2 (0.5)		1.76 (0.16-19.73)	0.649
T Total			0.003		
T1a	50 (52.6)	160 (38.5)		1	
T1b	17 (17.9)	136 (32.7)		0.4 (0.22-0.73)	0.003
T2	17 (17.9)	94 (22.6)		0.58 (0.32-1,06)	0.077
T3a	8 (8.4)	23 (5.5)		1.11 (0.47-2.64)	0.808
T3b	0	0		NA	NA
T4a	3 (3.2)	2 (0.5)		4.8 (0.78-29.54)	0.091
T4b	0	1 (0.2)		NA	NA

OR — odds ratio; CI — confidence interval; MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; RAI — radioactive iodine; NA — not applicable

Table 7. *Logistic regression analysis demonstrating the predictors of lymph node metastasis (LNM) in differentiated thyroid cancer (DTC)*

	LNM		p-value	Univariate	
	Present (n = 85)	Absent (n = 426)		OR (95% CI)	p-value
Parameters	n (%)				
Sex (female/male)	60/25 (70.6/29.4)	356/70 (83.6/16.4)	0.005	2.12 (1.24–3.61)	0.006
Age at diagnosis (≥ 55/< 55 years)	18/67 (21.2/78.8)	94/332 (22.1/77.9)	0.856		
Unilateral/Bilateral	65/20 (76.5/23.5)	355/71 (83.3/16.7)	0.131		
Unifocal/Multifocal	49/36 (57.6/42.4)	305/121 (71.6/28.4)	0.011	1.85 (1.15–2.99)	0.012
Number of tumour foci			< 0.001		
1	49 (57.6)	305 (71.6)		1	
2	14 (16.5)	78 (18.3)		1.17 (0.59–2.13)	0.736
≥ 3	22 (25.9)	43 (10.1)		3.18 (1.75–5.78)	< 0.001
MTD (≤ 10/> 10 mm)	27/58 (31.8/68.2)	209/217 (49.1/50.9)	0.003	2.07 (1.26–3.39)	0.004
TTD (≤ 10/> 10 mm)	23/62 (27.1/72.9)	185/241 (43.4/56.6)	0.005	2.07 (1.24–3.46)	0.006
MTD, TTD, and focality			0.007		
Group 1 MTD ≤ 10 mm, unifocal, TTD ≤ 10 mm	20 (23.5)	162 (38)		1	
Group 2 MTD ≤ 10 mm, multifocal, TTD ≤ 10 mm	3 (3.5)	23 (5.4)		1.06 (0.29–3.84)	0.933
Group 3 MTD ≤ 10 mm, multifocal, TTD > 10 mm	4 (4.7)	24 (5.6)		1.35 (0.42–4.29)	0.611
Group 4 MTD > 10 mm, unifocal, TTD > 10 mm	29 (34.1)	143 (33.6)		1.64 (0.89–3.03)	0.112
Group 5 MTD > 10 mm, multifocal, TTD > 10 mm	29 (34.1)	74 (17.4)		3.17 (1.69–5.98)	< 0.001
Microscopic ETE (absent/present)	49/36 (57.6/42.4)	365/61 (85.7/14.3)	< 0.001	4.4 (2.64–7.31)	< 0.001
Macroscopic ETE (absent/present)	81/4 (95.3/4.7)	421/5 (98.8/1.2)	0.046	4.16 (1.09–1.58)	0.037
Vascular invasion (absent/present)	58/27 (68.2/31.8)	383/43 (89.9/10.1)	< 0.001	4.15 (2.38–7.22)	< 0.001
Lymphatic invasion (absent/present)	55/30 (64.7/35.3)	388/38 (91.1/8.9)	< 0.001	5.57 (3.2–9.71)	< 0.001
RAI need (absent/present)	19/66 (22.4/77.6)	213/213 (50/50)	< 0.001	3.47 (2.02–5.99)	< 0.001
BRAF mutation			0.096		
Positive	7 (8.2)	14 (3.3)			
Negative	6 (7.1)	25 (5.9)			
Unknown	72 (84.7)	387 (90.8)			
T			0.012		
T1a	29 (34.1)	210 (49.3)		1	
T1b	31 (36.5)	140 (32.9)		1.6 (0.92–2.78)	0.092
T2	19 (22.3)	57 (13.4)		2.41 (1.26–4.62)	0.008
T3a	2 (2.3)	14 (3.3)		1.03 (0.22–4.78)	0.965
T3b	0	0		NA	NA
T4a	2 (2.3)	4 (0.9)		3.62 (0.64–2.06)	0.148
T4b	2 (2.3)	1 (0.2)		14.48 (12.73–16.48)	0.031
T Total			0.001		

Table 7. *Logistic regression analysis demonstrating the predictors of lymph node metastasis (LNM) in differentiated thyroid cancer (DTC)*

	LNM		p-value	Univariate	
	Present (n = 85)	Absent (n = 426)		OR (95% CI)	p-value
T1a	24 (28.2)	186 (43.7)		1	
T1b	22 (25.9)	131 (30.8)		1.3 (0.7–2.42)	0.405
T2	30 (35.3)	81 (19)		2.87 (1.58–5.21)	0.001
T3a	6 (7.1)	25 (5.9)		1.86 (0.69–4.99)	0.218
T3b	0	0		NA	NA
T4a	2 (2.3)	3 (0.7)		5.17 (0.82–3.25)	0.08
T4b	1 (1.2)	0		NA	NA

OR — odds ratio; CI — confidence interval; MTD — maximum tumour diameter; TTD — total tumour diameter; ETE — extrathyroidal extension; RAI — radioactive iodine; NA — not applicable

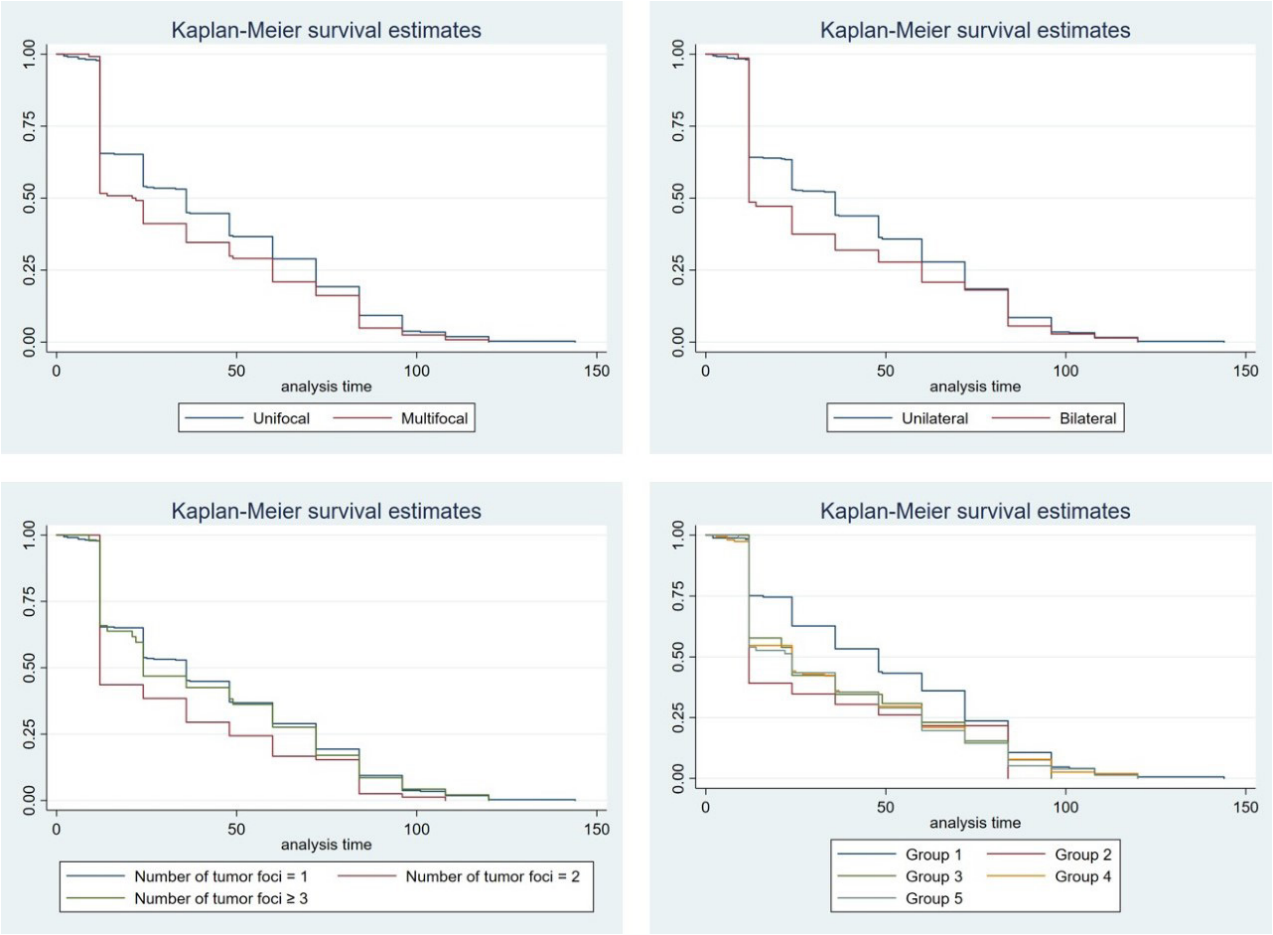

Figure 1. *Kaplan-Meier metastasis-free survival estimates of lymph node metastasis (LNM) according to focality, laterality, number of tumour foci, or group*

predictive value of 96.9%. We found a cut-off value of 14.5 mm for TTD in predicting LNM in the whole group. Studies analysing TTD in predicting recurrence or LNM with ROC analysis are limited in the literature. In our findings, a cut-off value of 14.5 mm is adequate in its discrimination of patients with lower MFS in DTC. In another study, the tumour diameter ratio (the ratio of the primary tumour to the TTD) was found to be a significant predictor of LNM in both the microcarcinoma and microcarcinoma groups, and ROC analysis indicated a perfect effect (AUC: 0.945 cut-off: ≤ 0.56, and AUC:0.998 cut-off: ≤ 0.57, respectively) [12].

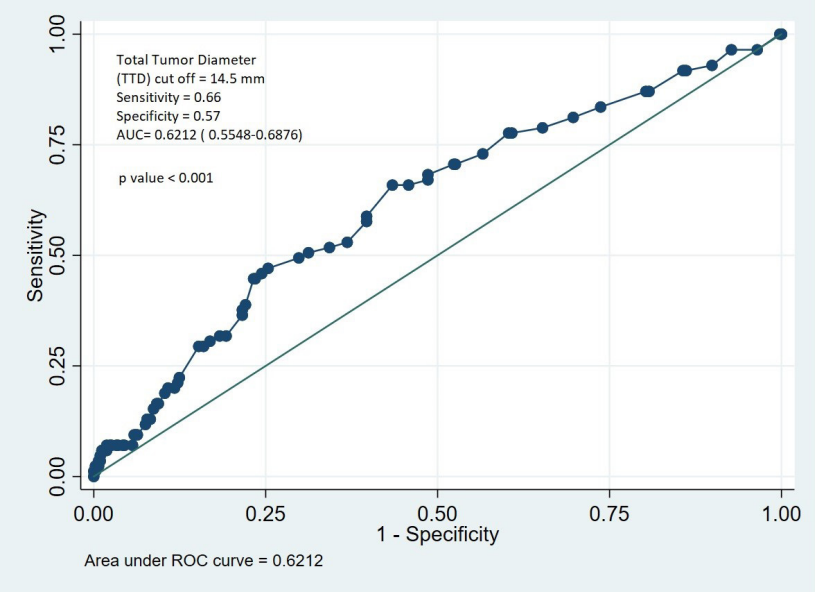

Figure 2. *Receiver operating characteristic (ROC) curve analysis indicating the cut-off value of total tumour diameter (TTD) to predict lymph node metastasis (LNM)*

Similarly to the literature, we revealed that the ratio of patients with macrocarcinoma or with TTD > 10 mm was higher in multifocal DTC than in unifocal DTC [11]. We showed that ATA risk category, vascular invasion, LNM at diagnosis, or RAI total dose was higher in Group 5 than in Group 3. In one study, there was no difference in the ratio of capsular invasion, ETE, LNM, lymphovascular invasion between multifocal microcarcinoma with a TTD > 10 mm, and the multifocal macrocarcinoma group [11]. In another study analysing 370 patients with PTC, the sum of tumour diameters of ≥ 40 mm, was seen to be a good predictor for RFS in multifocal disease, with a negative predictive value of 96.9% [5]. We propose that MTD is very important in the prediction of recurrence. However, analysis of MTD alone, independently of TTD, may lead to an unnoticed risk of recurrence or undertreatment. Based on these results, we cannot conclude that similar management strategies might be employed in multifocal microcarcinoma with a TTD ≤ 10 mm, multifocal microcarcinoma with a TTD > 10 mm, and unifocal macrocarcinoma findings alone. The management should be planned on a case-by-case basis by considering MTD, TTD, and focality along with other factors.

We also analysed the combined effect of focality, MTD, and TTD on PTC recurrence. We showed that the ratio of patients in Groups 1, 2, 3, 4, or 5 was similar whether there was recurrence or not. Based on our findings and the previous literature, the importance of TTD on DTC outcomes is suggested for future studies. The predictive value of TTD should be analysed in a subgroup such as that of microcancer or unilateral DTC. To detect TTD accurately, similarly to the detection of multifocality, we tend to perform TT. Besides, TTD may also be useful in the intraoperative decision of TT or in the postoperative follow-up of patients with DTC.

LNM was seen in 16.6% of the patients in our study, and multifocality increased the risk of LNM 1.85-fold in DTC. In one study analysing 305 patients with PTC, it was shown that multifocality did not predict LNM [9]. Multifocal PTC was detected in more than half of the patients (54%) in that study, and the ratio was higher than that in the general literature. Kuo et al. showed that LNM was higher in multifocal PTC than in unifocal PTC, in a large cohort of 2418 patients with PTC [27]. Similar findings were also reported in another report [10]. We showed that male sex, MTD or a TTD > 10 mm, the presence of multifocal macrocarcinoma, ETE, vascular or lymphatic invasion, or RAI need were significant predictors of LNM. In a study analysing 912 patients with PTC, age (> 45 years), ETE, MTD, focality, and tumour number were shown to be significant predictors for LNM [11]. This resulted in the development of a new model indicating that a combination of new factors, such as MTD and TTD, or MTD, TTD, and focality, were significant independent predictors for LNM [11].

Tam et al. presented a new parameter – tumour diameter ratio – which could predict LNM and aggressive features in multifocal PTC [12]. They defined the tumour diameter ratio (TDR) as the largest tumour diameter divided by TTD. As

expected, they showed a lesser TDR in multifocal microcarcinoma than in macrocarcinoma. Each 1% decrease in the TDR was found to be associated with a 1.24-fold higher risk of LNM in multifocal microcarcinoma ($p < 0.001$), and a 3.98-fold higher risk of LNM multifocal macrocarcinoma ($p = 0.015$). ROC analysis revealed that cut-off values for TDR in the prediction of LNM were 0.56 and 0.57 with a sensitivity of 100% in multifocal microcarcinoma (AUC: 0.945) and macrocarcinoma (AUC: 0.998), respectively. They also showed that TDR was an important predictor for ETE and capsular invasion [12]. These findings serve to provide an additional clinical predictor in the discrimination of those patients with the same primary tumour diameter. Although TDR seems to be a good predictor for aggressive features in DTC, it has been less studied.

Strength and limitations

We included a considerable number of patients with PTC in our study. The number of studies investigating multifocality, number of tumour foci, or laterality of tumours together with TTD is limited in the literature. We performed ROC analysis to find a cut-off value for TTD in the prediction of LNM, which was lacking in most previous studies. Our study was conducted retrospectively. We were only able to perform BRAF mutation analysis in approximately 10% of the patients. We performed TT in all patients included in the study, but the level of application of RAI was lower than that in previous studies. We showed that bilaterality, multifocality, number of tumour foci (≥ 3), MTD (> 10 mm), or TTD (> 10 mm) were not positive predictors of recurrence, in contrast to many studies.

Conclusion

We revealed that bilaterality, multifocality, MTD (> 10 mm), and TTD (> 10 mm) did not predict recurrence. However, multifocality, number of tumour foci (≥ 3), MTD (> 10 mm), and TTD (> 10 mm) increased the risk of LNM. Alongside the guidelines and these findings, management of PTC should be planned on a case-by-case basis. More light may be shed on the predictors for recurrence or LNM in subgroups such as microcarcinoma or unilateral DTC in subsequent studies. Based on a growing body of evidence, we propose that TTD, multifocality, or bilaterality may be important factors in new guidelines, staging, or risk stratification systems. Future studies should look to clarify the issue of clonality in multifocal PTC and investigate the combination effect of mutation analysis with TTD, MTD, focality, or laterality.

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